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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THERAPEUTIC COMPOSITIONS AND METHODS FOR TREATING DISEASE STATES WITH MYELOID PROGENITOR INHIBITORY FACTOR-1 (MPIF-1), MONOCYTE COLONY INHIBITORY FACTOR (M-CIF), AND MACROPHAGE INHIBITORY FACTOR-4 (MIP-4)

Additions	Concentration required for 50% of maximal LPP-CFC inhibition (ng/ ml)
MPIF-1, wild type	10-20
Mutant-1	15-25
Mutant-6	1-10
Preparation K0871	0.1-1.0
HG00300-B-7	0.1-1.0

(57) Abstract

There are disclosed therapeutic compositions and methods using isolated nucleic acid molecules encoding a human myeloid progenitor inhibitory factor-1 (MPIF-1) polypeptide (previously termed MIP-3 and chemokine β8 (CKβ8 or ckb-8)); a human monocyte-colony inhibitory factor (M-CIF) polypeptide (previously termed MIP1-γ and chemokine β1(CKβ1 or ckb-1)), and a macrophage inhibitory protein-4 (MIP-4), as well as MPIF-1, M-CIF and/ r MIP-4 polypeptides themselves, as are vectors, host cells and recombinant methods for producing the same.

What is claimed is:

1. A method of inhibiting proliferation or differentiation of myeloid progenitor cells, comprising administering to an individual an effective amount of a polypeptide selected from the group consisting of:

(a) a Myeloid Progenitor Inhibitory Factor-1 (MPIF-1) N-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the first 22 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues of SEQ ID NO:4;

(b) a MPIF-1 C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the last C-terminal amino acid residue but not more than the last 52 C-terminal amino acid residues of SEQ ID NO:4, wherein the N-terminal amino acid residue of said MPIF-1 C-terminal deletion mutant is amino acid residue 1 (Met) or 22 (Arg) of SEQ ID NO:4;

(c) a MPIF-1 N-terminal and C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the first 22 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues of SEQ ID NO:4 and a deletion of at least the last C-terminal amino acid residue but not more than the last 52 C-terminal amino acid residues of SEQ ID NO:4;

(d) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (a);

(e) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (b);

(f) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (c);

(g) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (a) except for at least one amino acid substitution;

(h) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (b) except for at least one amino acid substitution; and

(i) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (c) except for at least one amino acid substitution.

2. The method of claim 1, wherein said individual is human.

3. The method of claim 1, wherein the myeloid progenitor cells are low proliferative potential-colony forming cells (LPP-CFC).

4. The method of claim 1, wherein the myeloid progenitor cells are colony forming unit-granulocyte and monocyte cells (CFU-GM).

5. The method of claim 1, wherein said individual is undergoing therapy that kills dividing cells.

6. The method of claim 5, wherein said therapy is selected from chemotherapy or radiation therapy.

7. The method of claim 6, wherein said polypeptide is administered prior to said therapy.

8. The method of claim 7, further comprising administering a myelostimulator after said therapy.

9. The method of claim 8, wherein said myelostimulator is selected from the group consisting of Granulocyte-Colony Stimulating Factor, Granulocyte Macrophage-Colony Stimulating Factor, Interleukin-11, and Thrombopoietin.

10. The method of claim 6, wherein said administration of said polypeptide results in accelerated recovery of platelets or granulocytes.

11. The method of claim 10, wherein said accelerated recovery of platelets or granulocytes alleviates thrombocytopenia or neutropenia.

12. The method of claim 1, wherein said polypeptide is administered to treat a myeloproliferative disorder.

13. The method of claim 12, wherein said disorder is selected from the group consisting of essential thrombocytosis (ET), polycythemia vera (PV), and agnogenic myeloid metaplasia (AMM).

14. The method of claim 1, wherein said polypeptide is (a).

15. The method of claim 14, wherein said mutant has a deletion of at least the first 37 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues.

16. The method of claim 15, wherein said mutant has a deletion of at least the first 48 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues.

17. The method of claim 15, wherein said mutant has a deletion of at least the first 37 N-terminal amino acid residues but not more than the first 48 N-terminal amino acid residues.

18. The method of claim 17, wherein said mutant has an amino acid sequence as shown in SEQ ID NO:4 selected from the group consisting of: Leu (38) - Asn (120); Glu (39) - Asn (120); Leu (44) - Asn (120); Asp (45) - Asn (120); Arg (46) - Asn (120); His (48) - Asn (120); Ala (49) - Asn (120).

19 The method of claim 18, wherein said mutant has the amino acid sequence Asp (45) - Asn (120).

20. The method of claim 14, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

21. The method of claim 15, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

22. The method of claim 16, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

23. The method of claim 17, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

24. The method of claim 18, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

25. The method of claim 19, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

26. The method of claim 1, wherein said polypeptide is (d).

27. The method of claim 26, wherein said amino acid sequence is at least 97% identical to the amino acid sequence of said MPIF-1 N-terminal deletion mutant of (a).

28. The method of claim 27, wherein said amino acid sequence is at least 99% identical to the amino acid sequence of said MPIF-1 N-terminal deletion mutant of (a).

29. The method of claim 1, wherein said polypeptide is (g).

30. The method of claim 29, wherein said at least one amino acid substitution is selected from the group consisting of Asp (45) Ala; Asp (45) Gly; Asp (45) Ser; Asp (45) Thr; Asp (45) Met; Asp (53) Ala; Asp (53) Gly; Asp (53) Ser; Asp (53) Thr; Asp (53) Met; Ser (51) Gly; Ser (34) Gly; Pro (60) Thr; and Ser (70) Ala.

31. The method of claim 1, wherein said polypeptide is (b).

32. The method of claim 31, wherein said mutant has a deletion of at least the last 15 C-terminal amino acids but not more than the last 52 C-terminal amino acids.

33. The method of claim 32, wherein said mutant has a deletion of at least the last 20 C-terminal amino acids but not more than the last 52 C-terminal amino acids.

34. The method of claim 33, wherein said mutant has a deletion of at least the last 36 C-terminal amino acids but not more than the last 52 C-terminal amino acids.

35. The method of claim 34, wherein said mutant has a deletion of at least the last 41 C-terminal amino acids but not more than the last 52 C-terminal amino acids.

36. The method of claim 31, wherein said mutant has a deletion of at least the last 48 C-terminal amino acids but not more than the last 52 C-terminal amino acids.

37. The method of claim 31, wherein said amino acid sequence includes the amino acid Met added to the N-terminus.

38. The method of claim 1, wherein said polypeptide is (e).

39. The method of claim 38 wherein said amino acid sequence is at least 97% identical to the amino acid sequence of said MPIF-1 C-terminal deletion mutant of (b).

40. The method of claim 39, wherein said amino acid sequence is at least 99% identical to the amino acid sequence of said MPIF-1 C-terminal deletion mutant of (b).

41. The method of claim 1, wherein said polypeptide is (h).

42. The method of claim 41, wherein said at least one amino acid substitution is selected from the group consisting of Asp (45) Ala; Asp (45) Gly; Asp (45) Ser; Asp (45) Thr; Asp (45) Met; Asp (53) Ala; Asp (53) Gly; Asp (53) Ser; Asp (53) Thr; Asp (53) Met; Ser (51) Gly; Ser (34) Gly; Pro (60) Thr; Ser (70) Ala; Ala (21) Met; Thr (24) Ala; Lys (25) Asn; Asp (26) Ala; Glu (30) Gln; Glu (28) Gln.

43. The method of claim 1, wherein said polypeptide is (c).

44. The method of claim 1, wherein said polypeptide is (f).

45. The method of claim 1, wherein said polypeptide is (i).

46. An isolated polypeptide selected from the group consisting of:

(a) a Myeloid Progenitor Inhibitory Factor-1 (MPIF-1) N-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the first 22 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues of SEQ ID NO:4;

(b) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (a); and

(c) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (a) except for at least one amino acid substitution;

wherein the isolated polypeptide does not consist of an amino acid sequence as shown in SEQ ID NO:4 selected from Glu (39) - Asn (120); Leu (44) - Asn (120); Asp (45) - Asn (120); or Arg (46) - Asn (120); and

wherein the isolated polypeptide inhibits proliferation or differentiation of myeloid progenitor cells.

47. The isolated polypeptide of claim 46, wherein said polypeptide is (a).

48. The isolated polypeptide of claim 47, wherein said mutant has a deletion of at least the first 37 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues.

49. The isolated polypeptide of claim 48, wherein said mutant has a deletion of at least the first 48 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues.

50. The isolated polypeptide of claim 49, wherein said mutant has a deletion of at least the first 37 N-terminal amino acid residues but not more than the first 48 N-terminal amino acid residues.

51. The isolated polypeptide of claim 50, wherein said mutant has an amino acid sequence as shown in SEQ ID NO:4 selected from the group consisting of: Leu (38) - Asn (120); His (48) - Asn (120); and Ala (49) - Asn (120).

52. The isolated polypeptide of claim 47, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

53. The isolated polypeptide of claim 48, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

54. The isolated polypeptide of claim 49, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

55. The isolated polypeptide of claim 50, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

56. The isolated polypeptide of claim 51, wherein said amino acid sequence of said mutant includes the amino acid Met added to the N-terminus.

57. The isolated polypeptide of claim 46, wherein said polypeptide is (b).

58. The isolated polypeptide of claim 57, wherein said amino acid sequence is at least 97% identical to the amino acid sequence of said MPIF-1 N-terminal deletion mutant of (a).

59. The isolated polypeptide of claim 58, wherein said amino acid sequence is at least 99% identical to the amino acid sequence of said MPIF-1 N-terminal deletion mutant of (a).

60. The isolated polypeptide of claim 46, wherein said polypeptide is (c).

61. The isolated polypeptide of claim 60, wherein said at least one amino acid substitution is selected from the group consisting of Asp (45) Ala; Asp (45) Gly; Asp (45) Ser; Asp (45) Thr; Asp (45) Met; Asp (53) Ala; Asp (53) Gly; Asp (53) Ser; Asp (53) Thr; Asp (53) Met; Ser (51) Gly; Ser (34) Gly; Pro (60) Thr; and Ser (70) Ala.

62. The isolated polypeptide of claim 46, which is produced or contained in a recombinant host cell.

63. The isolated polypeptide of claim 62, wherein said host cell is *E. coli.*

64. The method of claim 1, wherein said polypeptide is administered together with a pharmaceutically acceptable carrier or excipient.

65. The isolated polypeptide of claim 46, together with a pharmaceutically acceptable carrier or excipient.

66. An isolated polynucleotide encoding a polypeptide of claim 46.

67. The isolated polynucleotide of claim 66, which is DNA.

68. A method of making a recombinant vector comprising inserting the polynucleotide of claim 66 into a vector.

69. A recombinant vector produced by the method of claim 68.

70. A method of making a recombinant host cell comprising introducing the recombinant vector of claim 69 into a host cell.

71. A recombinant host cell produced by the method of claim 70.

72. The isolated polypeptide of claim 46, which produced by a method comprising:

introducing a recombinant vector comprising a polynucleotide encoding said polypeptide into a host cell;

culturing said host cells; and

recovering said polypeptide.

73. A method for producing a polypeptide comprising:

culturing the recombinant host cell of claim 71 under conditions that said vector is expressed; and

recovering said polypeptide.

74. An isolated polypeptide selected from the group consisting of:

(a) a MPIF-1 C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the last C-terminal amino acid residue but not more than the last 52 C-terminal amino acid residues of SEQ ID NO:4, wherein the N-terminal amino acid residue of said MPIF-1 C-terminal deletion mutant is amino acid residue 1 (Met) or 22 (Arg) of SEQ ID NO:4;

(b) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (a); and

(c) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (a) except for at least one amino acid substitution.

75. An isolated polypeptide selected from the group consisting of:

(a) a MPIF-1 N-terminal and C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:4 having a deletion of at least the first 22 N-terminal amino acid residues but not more than the first 53 N-terminal amino acid residues of SEQ ID NO:4 and a deletion of at least the last C-terminal amino acid residue but not more than the last 52 C-terminal amino acid residues of SEQ ID NO:4;

(b) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said MPIF-1 deletion mutant of (a); and

(c) a polypeptide having an amino acid sequence identical to the amino acid sequence of said MPIF-1 deletion mutant of (a) except for at least one amino acid substitution.

76. An isolated polypeptide selected from the group consisting of:

(a) a N-terminal deletion mutant of a Myeloid Progenitor Inhibitory Factor-1 (MPIF-1) splice variant comprising an amino acid sequence of SEQ ID NO:11 having a deletion of at least the first 45 N-terminal amino acid residues but not more than the first 59 N-terminal amino acid residues of SEQ ID NO:11;

(b) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said mutant of (a); and

(c) a polypeptide having an amino acid sequence identical to the amino acid sequence of said mutant of (a) except for at least one amino acid substitution.

77. The isolated polypeptide of claim 76, wherein said polypeptide is (a).

78. The isolated polypeptide of claim 77, wherein said mutant has an amino acid sequence as shown in SEQ ID NO:11 selected from the group consisting of Met (46) - Asn (137); Pro (54) - Asn (137); and His (60) - Asn (137).

79. An isolated polypeptide selected from the group consisting of:

(a) a Monocyte Colony Inhibitory Factor (MCIF) N-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:2 having a deletion of at least the first 20 N-terminal amino acid residues but not more than the first 40 N-terminal amino acid residues of SEQ ID NO:2;

(b) a M-CIF C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:2 having a deletion of at least the last C-terminal amino acid residue but not more than the last 25 C-terminal amino acid residues of SEQ ID NO:2, wherein the N-terminal amino acid residue of said M-CIF C-terminal deletion mutant is amino acid residue 1 (Met) or 20 (Thr) of SEQ ID NO:2;

(c) a M-CIF N-terminal and C-terminal deletion mutant comprising an amino acid sequence of SEQ ID NO:2 having a deletion of at least the first 20 N-terminal amino acid residues but not more than the first 40 N-terminal amino acid

residues of SEQ ID NO:2 and a deletion of at least the last C-terminal amino acid residue but not more than the last 25 C-terminal amino acid residues of SEQ ID NO:2;

(d) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said M-CIF deletion mutant of (a);

(e) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said M-CIF deletion mutant of (b);

(f) a polypeptide having an amino acid sequence at least 95% identical to the amino acid sequence of said M-CIF deletion mutant of (c);

(g) a polypeptide having an amino acid sequence identical to the amino acid sequence of said M-CIF deletion mutant of (a) except for at least one amino acid substitution;

(h) a polypeptide having an amino acid sequence identical to the amino acid sequence of said M-CIF deletion mutant of (b) except for at least one amino acid substitution; and

(i) a polypeptide having an amino acid sequence identical to the amino acid sequence of said M-CIF-1 deletion mutant of (c) except for at least one amino acid substitution.

80. A method of treating an individual comprising administering to the individual an effective amount of the polypeptide of claim 79, wherein said polypeptide is administered for an indication selected from the group consisting of: (a) myeloprotection; (b) inhibiting growth of hematopoietic progenitor cells; (c) treating sepsis; (d) suppression of TNF-α production; (e) treating renal injury; (f) treating arthritis or joint inflammation; (g) treating enterocolitis; (h) treating lupus.

81. A method of treating an individual comprising administering to the individual an effective amount of an isolated polypeptide comprising a sequence selected from the group consisting of:

(a) amino acids 1-93 in SEQ ID NO:2;

(b) amino acids 20-93 in SEQ ID NO:2;

(c) an amino acid sequence at least 95% identical to the amino acid sequence in (a);

(d) an amino acid sequence at least 95% identical to the amino acid sequence in (b);

(e) an amino acid sequence identical to (a) except for at least one conservative amino acid substitution; and

(f) an amino acid sequence identical to (b) except for at least one conservative amino acid substitution; wherein

said isolated polypeptide is administered for an indication selected from the group consisting of: (a) treating sepsis; (b) suppression of TNF-α production; (c) treating renal injury; (d) treating arthritis or joint inflammation; (e) treating enterocolitis; and (f) treating lupus.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/17505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/19 C07K14/52 A61K38/19 C12N1/21 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 18228 A (FORSSMANN, W.G.) 6 July 1995 see sequences ID no.6 and 8 pages 12-13 see page 3, line 1 - line 4; claims ---	81
X	WO 95 17092 A (HUMAN GENOME SCIENCE) 29 June 1995 see claims; figure 8; examples 3,5,8,9 see page 18, line 1 - page 20, line 26 ---	81
A	WEBER M ET AL: "DELETION OF THE NH2-TERMINAL RESIDUE CONVERTS MONOCYTE CHEMOTACTIC PROTEIN 1 FROM AN ACTIVATOR OF BASOPHIL MEDIATOR RELEASE TO AN EOSINOPHIL CHEMOATTRACTANT" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, no. 2, 1 February 1996, pages 681-685, XP000609014 --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 1998	11.02.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018	Le Cornec, N

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 97/17505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POLTORAK A N ET AL: "MIP-1GAMMA: MOLECULAR CLONING, EXPRESSION, AND BIOLOGICAL ACTIVITIES OF A NOVEL CC CHEMOKINE THAT IS CONSTITUTIVELY SECRETED IN VIVO" JOURNAL OF INFLAMMATION, vol. 45, no. 3, 1995, pages 207-219, XP000647657 see the whole document ---	81
A	WO 96 16979 A (INCYTE PHARMACEUTICALS, INC.) 6 June 1996 see sequence ID no. 6 see claims ---	79-81
P,X	WO 97 12041 A (SMITHKLINE BEECHAM CORPORATION) 3 April 1997 see the whole document especially sequences ID.1-4 pages17-18 see claims ---	1,14,15, 17-19, 46-48
P,X	WO 97 15594 A (SMITHKLINE BEECHAM CORPORATION) 1 May 1997 see sequence ID no. 5 page 10, see the claims see sequence ID no.1 page 9 ---	1,46-48, 66-73, 79,80
P,A	WO 96 34891 A (HUMAN GENOME SCIENCE, INC.) 7 November 1996 see sequence ID no. 2 see claims see examples 11-13 -----	1-81

INTERNATIONAL SEARCH REPORT

In. .ational application No.
PCT/US 97/17505

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they *are* dependent claims and *are* not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 1-45, 64, 80-81 are directed to a method of treatment of the human/animal body (rule 39.1 IV PCT) , the search has been carried out and based on the alleged effects of the compound/composition.

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US 97/17505

1. Claims: 1-78

MPIF-1 mutant and method of treatment.

2. Claims: 79-81

M-CIF mutant and method of treatment.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/US 97/17505

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9518228 A	06-07-95	DE 4344397 A	06-07-95
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